Serologic measurement of hepatitis B virus cccDNA

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Description:

Background

Hepatitis B virus (HBV) infection is a global public health concern. Worldwide more than 350 million people are chronically infected with hepatitis B virus. HBV infection causes acute and chronic hepatitis leading to liver cirrhosis and hepatocellular carcinoma. After HBV infection, viral DNA is transferred to nuclei of the infected hepatocytes and the double-stranded, open circular DNA is converted to covalently closed circular DNA (cccDNA). Persistence of cccDNA remains an obstacle to clearing HBV in chronically infected people, who remain at risk of developing advanced liver disease. This is because cccDNA acts as a template for continued virion production in the hepatocyte nucleoplasm. As long as the infected hepatocyte survives, cccDNA remains in the nucleus, maintaining a viral ´pool´. Further, in patients undergoing antiviral therapy who discontinue treatment, HBV can reactivate from cccDNA. To monitor the persistence of cccDNA in the liver, repeated liver biopsies are required, which are hazardous and uncomfortable to the patient, and costly.

Previous studies have shown the presence of cccDNA in serum of chronically infected patients. Serum cccDNA levels correlate well with intrahepatic cccDNA content. Serum cccDNA may thus be used for sequential monitoring of intrahepatic cccDNA levels without the requirement for repeated liver biopsies. Further, the appearance of cccDNA in the serum can be a marker of liver damage.

Quantitative detection of cccDNA in serum thus has potential to evaluate the severity of liver damage and the efficacy of antiviral therapy. Methodologies for the detection of HBV cccDNA in serum have been reported but assays for its detection and quantification are not commercially available. Development of a facile quantitative assay is required for quantitative detection of cccDNA in peripheral blood, whose manufacture can be scaled up and marketed to diagnostic laboratories.

Project Goal

The purpose of this project is to identify a panel of sera from treated and untreated HBV-infected patients, validate and develop an assay for quantitative detection of cccDNA in serum or plasma, establish the performance characteristics of assay, and establish and validate the cccDNA detection kit.

Phase I Activities and Deliverables

1. Design assay for quantitative detection of HBV cccDNA in serum or plasma from HBV-infected patients.

2. Validate assay and determine sensitivity and specificity using seroconversion panels.

Projected Phase II Activities:

1. Validation of the assay using specimens from HBV-infected patients and controls; optimize and validate the assay using clinical samples from patients and controls and establish and improve performance characteristics of assay.

2. Validation of the assay using specimen from HBV infected patients and Report Writing; produce prototype HBV cccDNA assay and explore feasibility of transferring technology to commercial and state and public health laboratories.

Impact

After infection or antiviral therapy, HBV remains dormant in the infected person by adopting the cccDNA form in the liver. As cccDNA can also be found in the blood, especially after liver damage, its detection in serum or plasma allows the efficacy of antiviral therapy and the extent of liver damage to be evaluated without resorting to liver biopsies. Worldwide more than 350 million people are chronically infected with HBV. Improved antivirals are in the pipeline that potentially cure instead of suppress HBV. In the next 5-10 years, a substantial proportion of HBV infected persons who undergo antiviral therapy will benefit from access to a facile diagnostic method for the detection of cccDNA.

Commercialization Potential

Assays for detection and quantification of cccDNA in serum are not available. A simple, cost-effective and sensitive test kit, whose manufacture is then scaled up, should become marketable for use in diagnostic laboratories.